Risk Characterization Framework for Noncancer End Points

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The nature of both indoor air exposures and noncancer end points present significant issues for risk characterization. Noncancer end points are multidimensional, affecting various organs, and are assumed to have thresholds. Symptoms also vary in severity within a population. In addition to the complexity of noncancer risk assessment, indoor air exposures are typified by the presence of complex mixtures, which further complicates the complex nature of noncancer risk characterization. Most noncancer risk assessment efforts have focused on defining acceptable daily intakes or reference doses (RfD) rather than estimating incidence and severity of the wide range of effects within an exposed population. The risk characterization framework has been developed to accommodate the RfD approach but, more importantly, to address the multidimensional nature of noncancer risk characterization. Newly emerging methods and standard EPA risk assessment guidelines for noncancer effects and complex mixtures were used as guides for developing the framework. Information and data needs have been identified from the framework. Peak, average, and cumulative doses from indoor air exposures are highly dependent on variable indoor air concentrations and affected by time-activity patterns. Susceptibility also plays a significant role in noncancer end points and, unlike susceptibility in cancer risk assessment, is quantifiable. This paper highlights the risk characterization framework for noncancer health risks that we developed in cooperation with the U.S. Environmental Protection Agency Environmental Criteria and Assessment Office. Additionally, a preliminary application of the framework to a complex mixture of volatile organic compounds from indoor sources is illustrated.

Introduction

The Research Triangle Institute (RTI), in cooperation with the U.S. Environmental Criteria and Assessment Office, Research Triangle Park (ECAO-RTP), has developed a risk characterization framework to provide a systematic approach for analyzing and presenting study results that estimate the health risks for indoor air pollutants. The framework was initially developed for characterizing both carcinogenic and noncarcinogenic health risks. However, due to several substantive differences between these types of health risks, two separate frameworks have been developed. This paper presents the risk characterization framework for noncancer health risks and a preliminary application of the framework to a complex mixture of volatile organic compounds from indoor sources.

Noncancer Risk Characterization Framework

The risk characterization framework for noncancer health effects is presented in Figure 1. It provides a means to display the complexity of characterizing noncancer health effects, the issues involved, the data and information needs, and the relationship among these data elements and issues. The four elements of risk

assessment, hazard identification, exposure assessment, dose–response assessment, and risk characterization, are represented in the framework. The risk assessment process as represented in the framework is further subdivided into 10 elements (represented by columns B through K in Figure 1). This allows for greater detail in examining the overall risk estimation process. Hazard identification is covered in columns B through J of Figure 1 in a primarily qualitative manner; exposure assessment is covered by columns B through F, dose–response assessment by columns G and H, and risk characterization by columns I through K, though it actually integrates information from all previous steps. The framework has been subdivided into the four groupings at the top of the figure to exhibit data needs for characterizing exposure (columns $C–E$), dose (columns $E–G$), individual health effects (columns $G–I$) and population health effects (columns $I–K$).

The major elements of noncancer risk characterization are outlined and summarized below. The concepts and issues presented represent the ideal in terms of the information and data needed to conduct a thorough risk characterization of noncancer health effects. The issues and data needs presented in the framework include both standard EPA methods (for noncancer and complex mixture risk assessment) and state-of-the-art, emerging techniques. Typically, data are unavailable to use the sophisticated emerging methods, and standard EPA methods are relied upon. However, the ideal information needs have been presented to fully elucidate the dimensions of noncancer risk

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Source Factors (B)	Pollutant Concentration (C)	Exposure Duration/Setting (D)	Exposure (E)	Dosimetry Factors (F)	Dose (G)	Response Factor (H)	Individual Health Effects (I)	Exposed Population (J)	Population Health Effects (K)
AC Systems Ambient Air Building Mat Copying Mach. Earth or Ground Furnishing Gas Stoves Household Prod Insulation Heaters, Kerosene Tobacco Smoking Vehicle Exhaust Woodstoves Carpets	Organics Inorganics Biologicals Mixtures Peak Constant Variable Averaging Time	Short Duration Long Duration Micro-environments Outdoors Indoors Time Activity Patterns	Integrated by Direct Measur Calculated from Columns (C) and (D)	Contact Rate Absorption Rate Ave Body Weight Regional Surface Area of Lung Other Factors	Cumulative and/or Peak Pollutant Mass per Body Weight per Time or Pollutant Mass per Surface Area per Time	Non-Carcinogenic Potency Non-Carcinogenic Threshold Dose-Response Function • Multiple Organs • Multiple Symptoms Mixtures/Synergisms	"Adverse" Effect • Multiple Organs • Multiple Symptoms Severity of Symptom/Effect Impairment of Function	Infants Children Home School Adults Male Female Worker Homemaker Smoker Nonsmoker Other	Incidence Susceptibility
Hazard Identification									
Exposure Assessment			**Dose-Response**			**Risk Characterization**			
Risk Assessment									

FIGURE 1. Risk characterization framework for noncancer health effects. Note that column A has been intentionally omitted as it is not relevant to this paper.

characterization. As the major issues related to noncancer health effects is the nature of the effects themselves, discussion of the framework will start with the goals of the risk characterization, how individual and population health effects are described (columns *I–K* of Figure 1). Discussion will then focus on the other columns in order (columns *C–H*) and how the nature of noncancer health effects influences these components.

Risk Characterization

Characterization of noncancer health effects differs (colums *I–K* of Figure 1) from those of cancer in the breadth of effects covered and in the detail in which they are characterized. Cancer risks are typically characterized as the number of cases of cancer attributed to the exposure in question. However, noncancer effects consist of multiple end points each having varying degrees of severity. Additionally, not all individuals may be at risk, or specific varying susceptibilities may exist within a population. Risk for noncancer effects ideally would be expressed as distributions within a population by effect and severity rather than a single estimate of increased cases.

Individual Health Effects

The first important factor in characterizing noncancer risks is the nature of the health effects (column *I* in Figure 1). One of the major differences between cancer and noncancer effects is the concept of threshold. Most, if not all, noncancer effects are assumed to have a threshold below which no adverse health effect would result from exposure. By contrast, cancer effects are assumed to have no threshold, with any exposure adding to the excess individual risk. Coupled to thresholds is the question as to what constitutes an "adverse health effect." Effects can range in severity from a metabolic change with no observed change in the performance of the individual to (frank) clinical conditions and illness to death. The framework can present the wide range of effects predicted, including adverse effects as well as possible biological indicators of future effects or increased susceptibilities to other or later exposures.

Another characteristic of noncancer health effects is that multiple target organs and systems can be affected with a wide range of reported symptoms, effects, and severity. Although there are many types of cancer, cancer effects are defined as the presence

or absence of cancer. By contrast, noncancer effects vary greatly and may include diverse effects or symptoms.

This complexity in characterizing noncancer health effects is exemplified by a condition associated with indoor air exposures, sick-building syndrome (SBS). SBS has become a relatively common problem attributed to volatile organic compounds (VOCs), biological contaminants, and other pollutants, consisting of acute, nonspecific sensory irritation and other sensory effects. The World Health Organization (*1*) defined SBS symptoms to include *a*) eye, nose, and throat irritation, *b*) sensation of dry mucous membranes, *c*) erythema (skin irritation, redness), *d*) mental fatigue and headaches, *e*) high frequency of airway infections and cough, *f*) hoarseness and wheezing, *g*) itching and unspecific hypersensitivity, and *h*) nausea and dizziness. The variety of end points is apparent in this condition, affecting multiple organs (eye, respiratory, etc.) with varying severity (eye irritation to unspecific hypersensitivity).

There are temporal considerations in addition to the fact that there are multiple organs and effects. Cancer effects are typically removed from exposures by latency periods associated with the mechanisms of cancer, and therefore, cancer risks are defined on the basis of increased statistical probability of developing cancer. By contrast, for noncancer health effects, time to appearance of the effect and whether or not the effect is reversible or permanent are important. Effects may be immediate and tied directly to exposure, such as irritation, or may be delayed in appearance as in developmental or reproductive effects. Additionally, effects may be transient, such as irritation, or permanent, as in unspecific hypersensitivity.

The prediction of the incidence or manifestation of effect is not the final estimator of risk as in cancer. The severity of the effect, both in terms of intensity of response and in threat to the health of the overall organism is equally important. Severity as a threat to the whole organism is not amenable to direct quantitative measurement (*2*), though ordinal ranking schemes have been proposed to assess severity. Tallarida et al. (*3*) developed a ranking scheme based on a risk/benefit analysis of adverse drug reactions to develop ordinal rankings of disease states. Hartung and Durkin (*2*) have expanded on this concept by dividing severity ranking into two components, an empirical severity rating and a subjective severity ranking.

Typically, noncancer effects are not life threatening but are believed to affect the performance of an individual. Therefore, some measure of impaired function is desirable. These subjective rating values can be developed by polls and are likely to have great variation among individuals but may prove useful in quantifying function impairment of individual performance. Ideally, all values for adverse health effects presented in column *I* of Figure 1 should be for a standard individual (e.g., a sensitive individual, or a lower 10th or upper 95th percentile within the population) for each organ affected and include a measure of the intensity for each effect. These values can then be used as a benchmark to calculate population effects. This information would be presented for each pollutant being evaluated and, if possible, for the overall mixture.

Affected Population

Individual responses vary greatly within a population (column *J* of Figure 1). The susceptibility of an individual to a specific

adverse effect dictates the level of a response. Individual susceptibilities are believed to follow some statistical distribution within a population. Additionally, susceptibility may be rooted in personal behavior, activities, and exposures associated with those activities. Individual sensitivities are distributed among a population and can include sensitive subpopulations (e.g., children in the case of low-level lead exposure), genetic predispositions (e.g., enzyme deficiencies), other exposures (e.g., smoking), preexisting conditions (e.g., asthma), and illness.

It is desirable to characterize exposed populations in column J on the basis of their sensitivities. This is above and beyond what is typically done for cancer risk assessment. Calculation of population risks would, therefore, have to correlate information on specific susceptibility and disease. The prevalence of specific susceptibilities within a population would identify the affected portion of the exposed population and would be presented in column J. Information presented in this column would include the distribution of general susceptibility for each effect.

Population Health Effects

Population risk estimates would be presented in column K of Figure 1 as the distribution of effects and severity within the population. Population incidence estimates are derived from individual response data, information on the distribution of susceptibility, and data on specific susceptibilities.

Exposure Assessment

Noncancer effects are generally tied more directly to actual exposure patterns and the associated dose than are cancer effects. As a result, greater detail is desirable for the exposure assessment. The details needed for conducting exposure assessments of noncarcinogens are discussed below and follow the organization of the columns of the framework shown in Figure 1.

Pollutant Concentration. Some indoor air pollutant sources are constant, resulting in an equilibrium with regard to pollution concentrations (column C of Figure 1). In such cases, a single value for pollutant concentration, determined by direct measurement or estimated from models, can be used to calculate exposure. However, most indoor air pollutant concentrations are transitory or episodic and are dependent on the pollutant source, its use and environmental and building conditions. Indoor air concentrations due to an individual source or activity (use) would tend to follow one of the general profiles shown in Figure 2. The actual shape of the decay curve is dependent on emission rate, temperature, humidity, and ventilation. The duration of the profile may vary greatly from several days or weeks (e.g., carpet installation or other building renovations) to minutes (e.g., use of household products). The overall concentration profile would be the aggregate of all individual profiles.

Dose–response modeling for noncancer effects generates a need for detailed concentration data as opposed to average concentrations. Ideally, information that should be included in column C are peak and average concentrations (either from measurement or model estimation) and, if possible, a concentration profile.

Averages may also prove useful, but the selection of the appropriate averaging time can be critical to the characterization
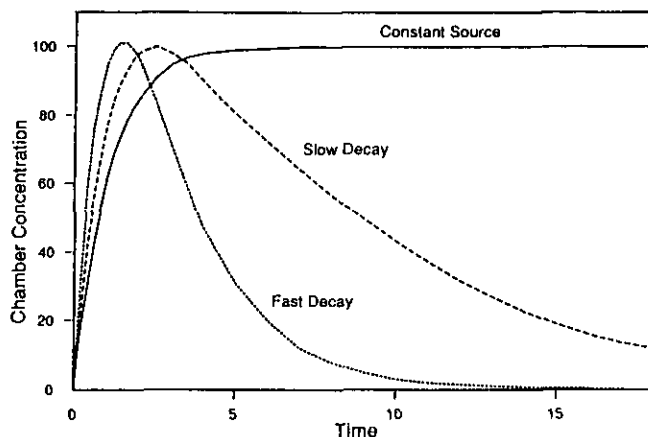

FIGURE 2. Concentration decay profiles. From Tichenor (4).

of health effects. For example, peak concentrations may be reported in various time increments such as hourly averages, 15-min averages, or 8-hr averages, each having different associated health effects. Averages may also prove useful in defining exposures associated with certain activities or events allowing total exposure to be calculated on the basis of number of events.

Exposure Duration/Setting. Defining microenvironments, the time individuals spend in each microenvironment, and the activities they are engaged in are important factors for determining the individual's exposure and the associated noncancer effects (column D of Figure 1). The timing of an exposure is important when concentrations are variable over time, as in the decay profile of off-gassing from new building materials. Coupled with variable concentrations (e.g., those undergoing a decay profile) are intermittent exposures as individuals move from one microenvironment to another. In these instances, the average concentration is inadequate to calculate total exposure. Therefore, actual exposures within different microenvironments must be integrated to obtain a realistic overall exposure to then calculate cumulative dose.

Activities are important to define or identify all relevant exposures, which may prove important in addressing mixtures and synergisms. It is conceivable that seemingly unrelated activities may actually be responsible for the onset of an adverse health effect. One activity may result in exposure to a compound that increases individual susceptibility to a compound associated with a later activity. Time-series analysis techniques may prove useful to address this by providing information on temporal distributions and correlating symptoms, exposure, and environmental parameters (5).

Information presented in column D would include quantitative descriptors of any relevant time-activity patterns including duration and time of occurrence for any exposure. Information would also be included from other exposures or activities to account for synergisms or sensitivities.

Exposure Pattern. Exposure is represented as not only an overall average value but several relevant values. Cumulative exposure and peak exposures (possibly over several averaging times) are recorded in column E of Figure 1 for each of the pollutants. These exposure estimates may be derived from direct

monitoring data or through indirect methods such as integrating time–activity pattern data with pollutant concentrations in the various microenvironments. Peak exposures are important for comparison to threshold values and certain dose–response functions. Also, the timing of exposures with respect to each other may be an important aspect of the exposure pattern when one is concerned with sensitization.

Dose–Response Assessment

Dose–response assessments (columns F–H of Figure 1) for noncarcinogens have typically focused on the identification of a threshold below which no adverse health effects are observed and the derivation of exposure levels that are considered to protect human health based on these thresholds. Little attention has been directed to deriving dose–response relationships due primarily to the complexity of these relationships, including the need to address multiple end points, multiple organs, and varying degrees of severity (6).

Dose Assessment

Noncancer effects are organ specific, which may require greater emphasis on pharmacokinetic modeling and relevant conversion factors (column F of Figure 1) to calculate systemic dose or delivered dose to specific target organs. Dose is presented in column G of Figure 1, calculated as organ burden or as a total body dose, and presented for several time periods; as peak, cumulative, and/or average associated with a given activity. Biomarkers, if available, can also be used to estimate actual dose, reducing the need for detailed exposure profiles. Biomarkers provide no information on exposure patterns and sources of exposure, except for a small number of sources such as environmental tobacco smoke.

Information presented in column F would include relevant conversion factors, including pharmacokinetic factors. Information presented in column G would include peak, cumulative, and average dose, and, if possible, peak, cumulative and average organ burden. This information would be presented for each of the pollutants being evaluated.

Dose–Response Factors

Noncancer effects involve multiple target organs, each having its own dose–response relationship and range of effects of varying degrees of severity for each pollutant. Ideally, these multiple dose–response factors could be represented in column H of Figure 1. Additionally, indoor air problems are characterized by multiple compounds, each of which would have their own dose–response functions and may predict a range of severity of effects (6).

Toxicological data can typically be divided into three categories, quantal, graded, and continuous (7–9). Quantal data express incidence and are generally expressed in terms of numbers of individuals affected as a function of dose. Graded data, though not as commonly used, are a type of quantal data but also include judgment or measure of severity of adverse effects as a function of dose (7). For example, graded data may be expressed in terms of identifying pathologies (e.g., fatty infiltration in liver cells to liver necrosis). Continuous data represent the magnitude or intensity of a response within an individual and measures the change in some value of a biological indicator as a function of dose. All types of data can be fit into a dose–response model, though the actual models would differ (8). Therefore, the characterization of the risk is dependent on which type of data is used. The framework is flexible enough to accommodate all three types of dose–response data and their subsequent models.

Another element unique to noncancer effects is the concept of thresholds for adverse effects. While there is still substantial debate as to what effect should be the basis for defining a threshold (i.e., change in biological indicator or clinical effect), the existence of thresholds is not contested. These thresholds differ according to the organ and effect studied. The framework represents these thresholds either alone or as the benchmark for the dose–response relationship. The thresholds reported in column H can be more specific than the commonly used protective concentrations, which are based on threshold measurements such as acceptable daily intakes or reference doses (9). The RfD is an estimate (within an order of magnitude) of the daily exposure to the human population (including sensitive subpopulations) that is likely to be without appreciable risk of deleterious effect during a lifetime (10). By contrast, the thresholds used as response factors could be effect specific and may also be time dependent (e.g., short term, chronic, etc.).

The use of mathematical dose–response models for noncancer effects is not common, though such methods do exist. The methods proposed by Dourson et al. (7) and Crump (8) may be applied to estimate specific effects at given concentrations and to develop the "dose–response" thresholds discussed above. Additionally, some method of assessing mixtures, considering both additivity and interactions, is also needed. A "mixture" dose–response factor, should it prove possible, may be applied in column H of the framework.

Ideally, information presented in column H would include known thresholds as a function of duration of exposure. This is likely to be in a matrix format. Dose–response factors would also be presented for multiple organs and multiple effects. These factors would be presented for each of pollutants being evaluated. Should methods be developed, dose–response factors for mixtures or factors for adding effects from individual compounds would also be presented in column H.

Application to an Example Complex Mixture

The concepts and issues presented above represent the ideal information and data needs to conduct a thorough risk characterization of noncancer health effects. However, typically, this information is not available, nor are the dose–response factors available or accepted for noncancer effects. More typically, risk assessments are simplified due to data limitations. The framework will be applied to an example complex mixture to demonstrate its usefulness and to test each of the concepts and issues discussed above for a real problem.

Table 1 presents an example complex mixture of VOCs associated with a problem building. Employees experienced increased health complaints after building renovations and, in particular, the installation of certain building materials. Efforts

Table 1. Volatile organics found in example complex mixture.

Compound	Concentration, ppb[a]
Toluene	13.0–22.0
Ethylbenzene	3.7– 4.6
Xylene	4.7– 8.6
Cumene	4.1– 6.9
4-Phenylcyclohexene	70.7[b]
Dichlorobenzene	18.0–68.0
Formaldehyde	61.0[c]
Acetaldehyde	15.0[c]
Acetone	55.0[c]

[a]Range of concentrations represent the values from gas chromatography/ flame ionization detector (GC/FID) and gas chromatography/mass spectrometry (GC/MS). Measurements made on new stored materials and are assumed to represent the maximum exposure levels. From Burchette and Singhvi (17).

[b]4-PCH concentration from GC/FID, presence confirmed but no concentration quantified on GC/MS.

[c]Predicted concentrations at 0.1 air changes per hour due to other building materials (office partitions) using a model developed by the EPA, Air and Energy Engineering Laboratory (AEERL) in Research Triangle Park. From Tichenor (18).

have been made to characterize the exposure of the affected workers. Sampling the work environment as well as the emissions from building materials confirmed what is a typical indoor air problem, consisting of a mixture of multiple compounds. The first seven compounds listed in Table 1 were the major components identified in measurements taken from new material of the same batch stored within a warehouse. As off-gassing emissions from new products tend to decay over time, these measurement values are assumed to represent the maximum exposure levels. These compounds will be further evaluated and used in the characterization of noncancer risks. In addition, formaldehyde, acetaldehyde, and acetone have been identified as major constituents in other building materials used in the renovation, and concentrations represent estimated concentrations predicted by a model for worst-case building ventilation conditions.

Identification of Possible Health Effects

The initial efforts addressing health effects focused on a review of the TOXNET database for the compounds identified in Table 1. Searches were made for each of the 10 compounds in the following fields: human toxicity excerpts; populations at special risk; absorption, distribution and excretion; metabolism/metabolites; biological half-life; mechanisms of action; interactions; and threshold limit values (TLVs). The reported effects have been summarized and are presented in Table 2. Only observed human health effects were recorded to simplify the initial phase and to avoid introducing uncertainties associated with interspecies extrapolation.

The information presented in the matrix is not exhaustive, but is illustrative of the types of health effects reported. Most of the information in TOXNET is from occupational exposures at concentrations much higher than that associated with indoor air pollutants. These effects or symptoms are not necessarily expected with any exposure to a given compound, but only indicate the range of possible effects. It should also be kept in mind that other effects may be possible, but have not been identified or, if they have been identified, not reported in TOXNET.

This approach is limited by both reported information and the extent to which a compound has been studied. For example, comparing formaldehyde and 4-phenylcyclohexene (4-PCH), one would get the impression that formaldehyde is an important component and major contributor to health impacts from indoor air, whereas 4-PCH contributes nothing to these effects. While this may be true, study bias may be a more accurate explanation. Formaldehyde is one of the most studied compounds, having an extensive database, whereas no information is reported in TOX-NET on 4-PCH and, in fact, only recently have any toxicological tests (animal bioassays) been carried out on 4-PCH.

Comparison with Common Thresholds (Health Effects Benchmarks)

The next level of sophistication is to introduce quantitative or elements of thresholds dose-response. A commonly recognized threshold is that of TLVs for use in an occupational setting. Although there are many objections to applying TLVs to the general public exposure setting, TLVs have been used by a number of states to establish air toxics standards. TLVs should not be used indiscriminately as a protective level for all indoor exposures, but can be used for a gross appraisal of possible health effects. Another common threshold is the odor threshold. Odors have been hypothesized to play an important role in indoor air problems by bringing attention of the individual to any symptoms, linking the odor (source) with any symptoms, or leading to symptoms directly (11). TLVs and odor thresholds were found for all compounds except 4-PCH, for which only an odor threshold has been estimated, and are presented in Table 3. Observed concentrations were several orders of magnitude lower than their respective TLVs, and odor thresholds were exceeded for three compounds (acetaldehyde, formaldehyde, and 4-PCH).

Theoretically, comparison of observed concentrations to any existing thresholds can be made for individual compounds. These thresholds can be for a wide range of effects. However, there are few data available on thresholds for health effects at low concentrations (in a controlled setting) which represents a severe limitation to this approach.

Mixture Index Values

All of the previous approaches have focused on the individual compounds and their respective health effects. It is desirable to develop some method of assessing the mixture as a whole rather than the sum of its individual components (13). The EPA has recommended several approaches in their Complex Mixture Risk Assessment Guidelines (14). Based on the approaches suggested in the guidelines as well as a review of the literature of noncancer risk assessment, a proposed approach of using a mixture index value has been applied. There are several options for these mixture index values, which include: hazard index, margin of exposure, additivity (with relative potency), response addition, comparative potency and toxicity equivalent factors, total organics (or by chemical class), indicator compound concentrations, interactions, and tiered approach.

The hazard index, margin of exposure, and additivity assume additivity of effects, and involve the summation of health effects for individual compounds. Comparative potency is different in

Table 2. Summary of reported effects of various indoor air pollutants.

Effect	AcA	ACE	CUM	DCB	EtB	FOR	STY	TOL	XYL	4-PCH
Eyes										
Irritation	X	X		X	X	X	X	X	X	
Irritated mucous membranes						X	X	X		
Conjunctivitis	X	X					X		X	
Lacrimation	X				X	X				
Diplopia (double vision)		X								
Photophobia	X									
Nose										
Irritation		X		X	X	X	X		X	
Irritated mucous membrane	X					X	X	X		
Runny nose				X						
Respiratory										
Irritation		X			X	X	X	X	X	
Pharyngitis		X							X	
Throat irritation				X		X	X		X	
Bronchitis	X	X				X			X	
Coughing	X					X				
Shortness of breath						X				
Asthmatic reaction						X				
Pulmonary edema	X					X				
Central nervous system										
Tinnitis								X		
Headache				X			X	X		
Dizziness		X	X	X				X		
Depression							X			
Fatigue							X			
Confusion							X	X	X	
Drowsiness	X		X							
Vertigo		X	X	X			X			
Slowed reaction time		X							X	
Intoxication: euphoria			X							
Exhilaration		X						X	X	
Boastful, talkative		X								
Incoordination (ataxia)		X	X				X		X	
Anesthesia							X	X		
Edema							X			
Weakness				X			X			
Skin										
Erythema, irritation			X		X					
Dermatitis	X					X	X			
Blood										
Leukopenia					X			X		
Leukocytosis					X			X		
Macrocytosis								X		
Reduced erythrocytes								X		
Liver injury				X						
Miscellaneous										
Gastritis		X								
Nausea and vomiting		X								
Dysphagia (difficulty swallowing)						X				
Menstrual disorders								X	X	
Loss of weight				X						

[a]AcA, acetaldehyde; ACE, acetone; CUM, cumene (isopropylbenzene); DCB, dichlorobenzene; EtB, ethylbenzene; FOR, formaldehyde; STY, styrene; TOL, toluene; XYL, xylene; 4-PCH, 4-phenylcyclohexene. This table summarizes those human health effects reported in TOXNET for these compounds. Absence of symptoms does not inherently mean that these do not exist for a given compound, only that they were not reported in TOXNET. Differences in the number of symptoms reported may be due to the differences in available information because some compounds may have been extensively studied, while others have not been studied at all in the human population (e.g., 4-PCH).

that the toxicity of the mixture is assessed directly without attention to individual components and is based on the assumption that bioassays are applicable to human health prediction. Mixtures are compared on the basis of bioassay results (15). The total chemical class approach assumes little difference in relative potencies between compounds with the same chemical characteristics. The indicator compound approach assumes that a single compound is indicative or responsible for a large fraction of total health effects. Interactions are a formal approach for addressing the physiological effects individual compounds have on one another, either synergistically or antagonistically. The tiered approach integrates elements of previous approaches. It would have a ceiling threshold to protect against a severe (clinical) effect and a dose–response component to estimate the distribution of less severe effects at concentrations below the threshold.

Table 3. Comparison of observed concentrations to two example thresholds.[a]

Compound	Maximum observed concentration, ppm	TLV, ppm	Odor threshold, ppm[b]
Acetaldehyde	0.015	100	0.00011–2.23
Acetone	0.055	750	19.675–668
Cumene (isopropylbenzene)	0.0069	50	0.0008–1.3
Dichlorobenzene	0.068	75	2.0–30
Ethylbenzene	0.0046	100	2.0–200
Formaldehyde	0.061	1	0.05–49
Styrene	0.033	500	0.047–200
Toluene	0.022	100	2.14–70
Xylene	0.0086	100	0.08–40
4-Phenylcyclohexene	0.072	—	0.001–0.01[c]

[a]Conclusions: observed concentrations < TLVs for all compounds; observed concentrations > three odor thresholds.

[b]From Ruth (*12*).

[c]From unpublished reports.

These mixture index values may prove useful as either absolute or relative predictors of risk (or effects). To validate their usefulness, efforts must be undertaken to correlate the various index values with controlled human chamber studies at low exposures, with bioassay data, or with epidemiological data. Once a mixture index value is selected, it can then be used to rank various mixtures for toxic effects and allow manufacturers to assess the need for and effectiveness of mitigation measures.

Two mixture index value approaches have been applied to the example complex mixture, the hazard index and margin of exposure approaches. These have been applied to the example mixture for those constituents with EPA-verified inhalation RfDs and are summarized in Table 4. Both of these methods are related to the NOAEL based either on animal studies or human data. The margin of exposure for each individual substance (MOE_i) is defined as the ratio of the NOAEL of a compound to the exposure for that substance (*16*). The MOE_i is not a direct measure of risk; as the MOE_i approaches the value of 1, the level of concern for possible effects is increased. It is interpreted as the extent to which human exposures are below the observed NOAEL in the study species. Five compounds of the example mixture had verified inhalation RfDs. MOE_i values have been calculated for these compounds and are presented in Table 4. For the example complex mixture, the MOE_i values are all within an order of magnitude of each other and are several orders of magnitude

above their individual observed thresholds (NOAEL).

For a mixture, the MOE is sum of the MOE_i for the individual constituents for a given target organ. Individual MOE_i values should only be summed for the same target organ system. Three of the five compounds having inhalation RfDs have identified NOAELs for the central nervous system. Therefore, a mixture MOE for the central nervous system (MOE_{CNS}) can be calculated. The MOE_{CNS} was calculated as 560. This is interpreted as indicating that the exposures are about 560 times below the "threshold value for the mixture."

The hazard index approach is the most common method used for noncancer effects from mixtures and is suggested in the EPA Guidelines on Complex Mixtures (*12*). It is the accepted practice in Superfund risk assessments. The hazard index (HI) is the sum of the hazard index for individuals compounds (HI_i) for a given target organ. The hazard index for individual compounds is the ratio of exposure of a compound to the RfD. The RfD is defined by dividing the NOAEL for the most sensitive species by an uncertainty and modifying factor, which compensates for dose extrapolation, inter- and intraspecies variability, study design, and available data. Similar to the MOE approach, as HI_i values approach 1, the level of concern for possible health effects increases. Values exceeding 1 indicate that the RfD has been exceeded. The HI_i values calculated for those five compounds having verified inhalation RfDs vary from 0.032 for toluene to

Table 4. Index approach examples.

Compound (i)	Observed concentration, ppb	NOAEL, ppb	Study species	Organ/effect	MOE_i[a]	UF	RfD mg/m³	RfD ppb	confidence[b]	HI_i[c]
Acetaldehyde	15.0	66,000 (LOAEL)	Rats	Histopathological changes in respiratory tract	4400	3,000	0.04	22	M/L/L	0.682
Cumene	5.5	18,700 (LOAEL)	Rats	CNS, nasal irritation	3400	10,000	0.009	1.8	L/L/L	3.056
1,4-Dichlorobenzene	43.0	11,210	Rats	Urinary protein output increased liver, kidney weights	260	100	0.7	115	H/M/M	0.374
Toluene	17.0	40,000	Human	CNS (dizz, headache) eye, nose irritation	2350	100	2.0	533	M/M/M	0.032
Xylene	6.6	6,200	Human	CNS, irritation	940	100	0.3	69	M/M/M	0.096

[a]Margin of exposure (MOE): MOE_i = observed concentration/NOAEL; e.g., MOE_{CNS} = $[1/\Sigma(1/MOE_i)]$ = $[1/MOE_{CUM} + 1/MOE_{TOL} + 1/MOE_{XYL}]^{-1}$ = $[(0.000294) + (0.000425) + (0.00106)]^{-1}$ = 560 times below the observed threshold level.

[b]Confidence: study/database/RfD. H, high; M, medium; L, low.

[c]Hazard index (HI): HI_i = observed concentration/RfD (where RfD = NOAEL/UF); e.g., HI_{CNS} = ΣHI_i = $HI_{CUM} + HI_{TOL} + HI_{XYL}$ = 3.056 + 0.032 + 0.096. HI_{CNS} = 3.184 >> 1.

3.056 for cumene. This is interpreted as indicating that toluene exposure is at about 3% of the RfD, while cumene exposures are more than three times the RfD level.

Cumene would appear to be targeted as the major toxic component in the mixture using this method. However, care should be taken in interpreting the RfD, as it is not a single number estimate of threshold or risk. There are multiple components to an RfD. The single value for an RfD must be considered in light of the uncertainty factor used in its calculation and in its confidence designation. The confidence designation consists of three components and indicates confidence in study design (in which the NOAEL was identified), in the overall database, and in the overall RfD. It should be noted that the two compounds with the highest HI_i, cumene and acetaldehyde, are also those compounds with the greatest uncertainty factors and the lowest confidence designations. Therefore, in reviewing the mixture and relative importance of each constituent and in the overall index value, these qualitative aspects of uncertainty should be considered.

An overall mixture HI was calculated for the central nervous system (HI_{CNS}). The value of 3.184 indicates that the exposure is more than three times the estimated "mixture RfD" for CNS effects. However, it should be noted that the cumene, which, as described above, has the highest uncertainty and lowest confidence designation, contributes about 96% to the overall index value. Therefore, this uncertainty should be included in any interpretation of this index value. Although there is significant uncertainty in the RfD, this is a useful method for identifying and predicting some health (CNS) effects for the example mixture.

Conclusions

The noncancer risk characterization framework has shown promise. The initial efforts discussed here are preliminary and should lead to further development of noncancer risk characterization methodologies. The framework has proven to be a useful tool for displaying the complexity of noncancer risk characterization, integrating information for the various components of a risk assessment from several sources, and evaluating data and information.

The framework (as depicted in Figure 1) lists the key issues specific to noncancer risk characterization. It displays the data and information needs to properly address noncancer health effects. Noncancer risk characterization differs from cancer risks primarily in the fact that noncancer health effects are multidimensional, with a wide range of health effects of varying severity affecting multiple organs. Columns I-J of the framework (Fig. 1) display the desired end points in noncancer health effects characterization and how the effects should characterized. Columns C-H of the framework (Fig. 1) show the data and information needs to carry out such a characterization.

The framework provides a formal mechanism to integrate information from several sources relating to exposure, dose response, and health effects. This was demonstrated in the application to the example complex mixture in which the framework facilitated the organization of data for source characterization, for constituents and their respective concentrations (Table 1), corresponding to columns B and C (Fig. 1), and for individual health effects reported in the exposed population and in the literature (e.g., Table 4), corresponding to columns I-K of Figure 1.

Following from the integration of information, the framework is also useful in evaluating the existence and quality of data and information. Related to the example complex mixture, existing data were available for columns B and C, pollutant source and concentration, and for columns I-K, individual health effects, exposed population, and population health effects. All data are considered to be preliminary and limited. Pollutant concentrations represent a maximum value off-gassing from the source and do not represent actual exposures. Health effects in the exposed population are limited to self-reported symptoms of an anecdotal nature with few data on incidence in the overall population.

Several major data gaps are apparent from reviewing available information. There is a lack of data on exposure duration/setting (column D), exposure (column E), dose conversion factors (column F), dose–response factors (column H). Maximum concentrations are presented with little information on the actual concentrations of exposure and time–activity patterns for the exposed population, which limits the calculation of exposure and dose. Also, there are limited data on noncancer dose–response factors, though this is an area receiving significant attention.

Preliminary efforts in developing and applying the framework have proven successful, though there is still a need for further refinement. The framework displays the complexity of the risk characterization process and the variety of data needs. It is useful in defining research needs and strategies (as in identifying the data gaps above) to obtain necessary data. The framework is particularly useful in pointing out data needs in a variety of disciplines and how these data need to be integrated to obtain a complete risk characterization. Such an approach can help to develop research strategies that are multidisciplinary and address the full range of issues relating to noncancer risk characterization.

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